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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/640,041	08/15/2000	W. Michael Kavanaugh	1615.002/200130.503	2270

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Chiron Corporation
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94662-8097

EXAMINER
JAMROZ, MARGARET E

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 02/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/640,041	KAVANAUGH ET AL.	
	Examiner	Art Unit	
	Margaret E Jamroz	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 November 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *10-13 and 15-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's amendment, filed 11/29/2001 (Paper No. 9), is acknowledged.

Claims 1-37 are pending.

Applicant's election of Group II (claims 1-9 and 14) in Paper No. 9 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 10-13 and 15-37 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a non-elected invention.

Claims 1-9 and 14 wherein the isolated nucleotide nucleic acid molecule comprising a polynucleotide which encodes SEQ ID NO: 4 and the nucleic molecule is SEQ ID NO: 3 are under consideration in the instant application.

2. Applicant should amend the first line of the specification to indicate priority is claimed under 35 U.S.C. 119e to provisional application 60/149,986.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112.

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-9 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claim 1 is indefinite for reciting "from about 1 to about 115 of SEQ ID NO: 4" in lines 7-8, and for reciting "from about 2 to about 115 of SEQ ID NO: 4" in lines 9-10. It is unclear how many amino acids constitute "about". One of skill in the art would not know if applicant meant one amino acid, as many as 40 amino acids, or even more.

6. Claim 2 is indefinite for reciting "an isolated nucleic acid molecule comprising about 345 contiguous nucleotides from the coding region of SEQ ID NO: 3" in lines 1-2. It is unclear how many amino acids constitute "about". One of skill in the art would not know if applicant meant a difference of one amino acid, as many as 40 amino acids, or even more.

7. Claim 3 is indefinite for reciting "from about 1 to about 115 of SEQ ID NO: 4" in line 6, and for reciting "from about 2 to about 115 of SEQ ID NO: 4" in line 7. It is unclear how many amino acids constitute "about". One of skill in the art would not know if applicant meant one amino acid, as many as 40 amino acids, or even more.

8. Claim 14 is indefinite for depending on non-elected claim 13.

9. Claim 14 is further indefinite for reciting a composition comprising an isolated polynucleotide. Base claim 13 recites a composition comprising an isolated polypeptide.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-9 and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid molecule comprising SEQ ID NO: 3 which encodes a polypeptide comprising SEQ ID NO: 4, a method of making a recombinant vector comprising inserting SEQ ID NO: 3 into a vector in operable linkage to a promoter, a recombinant vector comprising SEQ ID NO: 3, a method of making a recombinant host cell comprising inserting the vector comprising SEQ ID NO: 3, a recombinant host cell thereof, and a method of producing the polypeptide of SEQ ID NO: 3 comprising culturing the host cell, a composition comprising SEQ ID NO: 3 in a pharmaceutically acceptable excipient to identify homologous genes, hybridization, amplification, making recombinant EGFH2 and recombinant EGFH2 fusion proteins, and production of transgenic and knockout mice, and wherein the polypeptide of SEQ ID NO: 4 can be used as an immunogen to make antibodies which specifically bind SEQ ID NO: 4 for detection and immunoprecipitation, and wherein the polypeptide of SEQ ID NO: 4 can be used to screen peptide libraries, and in a yeast two-hybrid screening assay, does not reasonably provide enablement for an isolated nucleic acid molecule comprising a polynucleotide at least 90% identical to SEQ ID NO: 3; or any isolated nucleic acid molecule comprising any polynucleotide encoding any polypeptide wherein "except for at least one conservative amino acid substitution", said polypeptide has any amino acid sequence consisting of any sequence other than SEQ ID NO: 4, and wherein the isolated nucleic acid molecule is any sequence other than SEQ ID NO: 3, or the use of SEQ ID NO: 3 for gene therapy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification does not enable one of skill in the art to practice the invention as claimed without undue experimentation.

Applicant has not taught how to make or use an isolated nucleic acid molecule comprising a polynucleotide at least 90% identical to the polynucleotide as recited in claim 1f; encoding amino acids from about 1 to about 115 of SEQ ID NO: 4 as recited in claims 1c and 3; or from about 2 to about 115 of SEQ ID NO: 4 as recited in claims 1d and 3; the complement of the polynucleotide of 1c or 1d; any isolated nucleic acid molecule comprising the coding region of SEQ ID NO: 3 which is 348 nucleic acids as recited in claim 2; any of these isolated nucleic acid molecules which are anything other than DNA as recited in claim 4 as claimed. All of the depending claims 5-9, therefore, have these same problems. Applicant has not taught

any composition comprising an isolated polynucleotide encoding amino acids from about 4 to about 50 or from about 9 to about 45 of SEQ ID NO: 4 as recited in claim 13.

The claims as written encompass a broad genus of polypeptides with an unlimited number of possibilities with regard to the length of the polypeptide sequence. Further, making changes to up to 10% of a polynucleotide sequences does not provide that the encoded protein will retain the same function as the unmutated polynucleotide. Further, claim 3 as written encompasses a polypeptide wherein up to 100% of the amino acid residues have been changed with a conservative substitution because the recitation of "at least one conservative amino acid substitution" does not have an upper limit as to the number of residues changed. Consequently, SEQ ID NO: 4 with 100% of the residues substituted would not be encoded by the same nucleic acid sequence as SEQ ID NO: 3. One of ordinary skill in the art cannot envision all of the nucleic acid and amino acid substitutions encompassed by the breadth of the claims or all of the isolated nucleic acid molecule that encode from about 1 to about 115 of SEQ ID NO: 4 or from about 2 to about 115 of SEQ ID NO: 4. Additionally, nucleic acids must be inserted into a vector in-frame for the protein to be expressed; therefore, a polynucleotide which encodes from *about* 1 to *about* 115 or from *about* 2 to *about* 115 of SEQ ID NO: 4 as recited in claims 1 and 3, and a polynucleotide which encodes from *about* 4 to *about* 50 or from *about* 2 to *about* 49 of SEQ ID NO: 4 as recited in claim 13 would not be in the correct frame depending on which codon was first encoded by the various polynucleotides.

Skolnick and Fetrow (Trends in Biotechnology, 2000. 18(1): 34-39) teach that determining the sequence of a nucleic acid molecule does not provide sufficient information to obtain the structure of a protein. Furthermore, the function of a protein cannot be determined simply by knowing the structure of a protein, as many proteins are multifunctional. Changes in nucleic acid sequences can, therefore, potentially result in changes in essential three-dimensional structures of the given protein, and consequently, it's function.

It is known in the art that even single amino acid changes or differences in a proteins amino acid sequence can have dramatic effects on the protein's function. For example, Mikayama et al. (PNAS, 1993. 90: 10056-10060) teach that the human glycosylation factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (see Figure 1 in particular). Yet, Mikayama

et al. further teach that GIF is unable to carry out the function of MIF and MIF does not demonstrate GIF activity (see Abstract in particular).

Applicant is relying upon certain biological activities and the disclosure of a single species to support an entire genus. It is well known that minor structural differences among even structurally related compounds or compositions can result in substantially different biology, expression, and pharmacology of proteins. Therefore, structurally unrelated nucleic acids having or encoding " at least 90%" or "from about 1 to about 115 of SEQ ID NO: 4 or from about 2 to about 115 of SEQ ID NO: 4" encompassed by the claimed invention other than "nucleic acids set forth by SEQ ID NO: 3" would be expected to have greater differences in their activities. Since the amino acid sequence of a polypeptide determines its structure and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality requires knowledge of, and guidance with regard to, which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification) and detailed knowledge of the ways in which a polypeptide's structure relates to it's functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence and in turn utilizing predicted structural determinations to ascertain binding or functional aspects of EGFH2, and finally, what changes can be tolerated with respect thereto is complex and well outside the realm of routing experimentation.

It is known in the art that gene therapy and cancer therapy do not work. Anderson (Nature 1998; 392(Supp): 25-30) teaches that "the efficiency of gene transfer and expression in human patients ... is disappointingly low ... and that there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human disease" see page 25, left column, paragraph 1 in particular). Spitler (Cancer Biotherapy 1995; 10(1): 1-3) teaches that "cancer vaccines don't work" and that "there is no vaccine for therapy of cancer which has been approved by a regulatory agency for marketing in this or any other country" (see page 1, left column in particular)

In re Fisher, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which derivatives will retain functionality

requires knowledge of, and guidance with regard to, which amino acids in the polypeptide's sequence contribute to its structure, and therefore, function. The problem of predicting which derivatives of a protein will retain functionality and which will not is complex and well outside the realm of routine experimentation. Because of the lack of sufficient guidance and predictability in determining which nucleic acid sequences encode EGFH2 structures and would lead to functional EGF2 proteins with the desired properties and that the relationship between the sequence of a peptide and it's tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al, in The Protein Folding Problem and Tertiary Structure Prediction, 1994. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.); it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of proteins encompassed by the claimed invention.

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

12. Claims 1-9 and 14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of an isolated nucleic acid molecule comprising SEQ ID NO: 3 which encodes a polypeptide comprising SEQ ID NO: 4, a host cell with a vector comprising SEQ ID NO: 3, a method of making SEQ ID NO: 4 using said host cell, and a composition comprising an isolated polynucleotide comprising SEQ ID NO: 3 for identification of homologous genes, hybridization, amplification, making recombinant EGFH2 and recombinant EGFH2 fusion proteins, and production of transgenic and knockout mice. Applicant is further in possession of SEQ ID NO: 3 which encodes SEQ ID NO: 4 which can be used as an immunogen to make antibodies, and diagnostic assays, such as peptide library screening and yeast two-hybrid screening, and wherein the antibodies which specifically bind to SEQ ID NO: 4 can be used to detect and/or immunoprecipitate the polypeptide of SEQ ID NO: 4.

Applicant is not in possession of any nucleotide sequence which is 90% identical to SEQ ID NO: 3, about 345 contiguous amino acids of SEQ ID NO: 3, any polynucleotide other than SEQ ID NO: 3 which encodes any amino acid sequence other than SEQ ID NO: 4, any complement of a polynucleotide other than to SEQ ID NO: 3,or any nucleotide sequence which has been mutated so that at least one conservative amino acid substitution has been made which encodes SEQ ID NO: 4, any other polynucleotide to be used in a vector to be placed in a host cell to produce any polypeptide other than SEQ ID NO: 4, or any polynucleotide to be used for *in vivo* gene therapy.

Applicant has disclosed a single human nucleic acid sequence (SEQ ID NO: 3) which encodes a single human polypeptide (SEQ ID NO: 4); therefore, the skilled artisan cannot envision all the contemplated nucleic acid and/or amino acid sequence possibilities recited in the instant claims. Consequently, conception in either case cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The sequences themselves are required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993). The sequence itself is required. A description of a genus of polynucleotide sequences may be achieved by means of a recitation of a representative number of nucleotide sequences, defined by nucleic acid sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. Regents of the University of California v. Eli Lilly&Co., 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

13. The drawings are objected to because of the errors listed on the PTO-948; therefore, the drawings fail to comply with 37 CFR 1.84.

The Patent and Trademark Office no longer makes drawing changes. See 1017 O.G. 4. It is applicant's responsibility to ensure that the drawings are corrected. Corrections must be made in accordance with the instructions below.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be

allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in **ABANDONMENT** of the application.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Megan Jamroz, whose telephone number is (703) 308-8365. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Margaret (Megan) Jamroz, Ph.D.
Patent Examiner
Technology Center 1600
February 6, 2002

Christina Chan
CHRISTINA Y. CHAN
SUPERVISORY PATENT EXAMINER
GROUP ~~1800~~ 1640